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BY LEONARD ROGERS, M.D., F.R.C.P., F.R.C.S., I.M.S.

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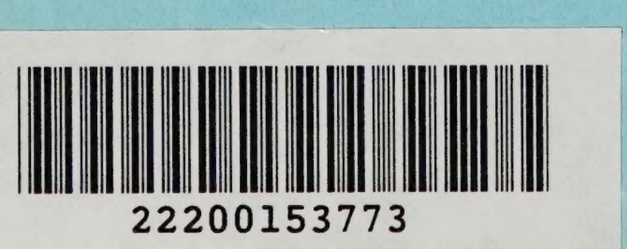
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# *The Variations in the Pressure and Composition of the Blood in Cholera; and their Bearing on the Success of Hypertonic Saline Transfusion in its Treatment.*

By LEONARD ROGERS, M.D., F.R.C.P., F.R.C.S., I.M.S., Professor of Pathology Calcutta.

(Communicated by Sir T. Lauder Brunton, Bart., F.R.S. Received December 4, 1908,—Read January 28, 1909.)

During the quarter of a century which has elapsed since the discovery by Prof. Koch of the comma bacillus of cholera, research work has been almost confined to the bacteriology of the subject. Unfortunately, with the exception of M. Haffkine's prophylactic inoculations, which are now very little used even in India, this line of work has done little or nothing to help the practitioner who is confronted with the treatment of this terrible disease. No powerful antitoxic serum of practical value has been produced, and even if such should still be obtained, many patients come under treatment in such a state of collapse that no medicine can be absorbed, even if retained.

The old controversy between the evacuant and conservative methods of treatment has long since ended in the practically universal adoption of the latter, although as late as 1866 Dr. George Johnson advocated castor oil, denying that there was any relationship between the amount of fluid lost from the body and the mortality, while he strenuously opposed the use of intravenous saline injections to replace it. There is still much difference of opinion about the latter treatment, for although all who have used transfusions testify to the remarkable immediate improvement in the pulse and general condition, yet this is commonly of such brief duration that many think it only serves to needlessly prolong the agony of the patient, so that of recent years it has been only exceptionally resorted to in India.

For a long time I have been investigating the blood changes in cholera (1), in the hope of finding some indication for a more rational and successful line of

treatment, than the mere administration of more or less useful drugs, into a gastro-intestinal tract, which is too congested to retain any appreciable powers of absorption. The great loss of fluid from the blood was shown by marked increase of the number of red corpuscles per cubic millimetre, which sometimes rose from 5,000,000 to over 8,000,000, while, like others, I found leucocytosis to be constantly present, and when of a marked degree to be of bad prognostic value. Differential counts showed a great decrease of the lymphocytes, corresponding with their accumulation in the lymphoid tissue of the alimentary tract, while the large mononuclears were markedly increased, both relatively and absolutely, this change being in proportion to the mortality, indicating its probable relationship to some specific toxin of the disease. These changes were often of great value in the difficult diagnosis of cholera from ptomaine poisoning, as I have not found them in the latter affection.

More recently I have studied the blood-pressure in cholera as an indication for the necessity of transfusion and the quantities to be injected. My first experiments in this line were carried out in conjunction with Captain J. W. D. Megaw, I.M.S. (2), who was in charge of the cholera patients at the Calcutta Medical College, normal saline solution (1 drachm to the pint) being used in accordance with the general custom. The patients were nearly all natives of India, whose normal blood-pressure averages only about 100 mm., being thus considerably lower than that of Europeans. In cholera, the pressure was rarely over 50 mm. on the admission of the patients, while in many it was too low to be estimated in the radial artery, owing to absence of any pulse at the wrist. We found that 1 pint of saline solution injected into a vein usually had very little effect in raising it, but a second pint generally increased it to 90 mm. or more. The immediate effects of this treatment were little short of marvellous. The terrible restlessness and cramps disappeared, and the worn out patient often fell asleep before its completion. The pulse was fully restored, and the blueness and coldness were replaced by the normal pink hue of the lips and nails and warmth of the extremities. A few improved steadily from that time, but only too frequently within 2 to 12 hours the copious rice water stools and vomiting recurred, and the patient relapsed into as bad a condition as before, with complete loss of the improvement in the blood-pressure. Repeated transfusions usually failed to save such patients, and although the mortality did show some reduction during the year Captain Megaw continued them, yet the disappointments were so many that the method soon came to be adopted only in a few desperate cases, and was eventually almost entirely abandoned once more, as it had been by so many earlier enthusiasts.

On thinking over the causes of this comparative failure, the following possible explanation occurred to me. The great loss of fluid through the stomach and bowels produces a concentration of the blood, which might be expected to increase the proportion of salts it contains, and therefore present a greater osmotic resistance to further draining off of fluid through the damaged intestinal mucous membrane. Thus, a conservative process, tending to check the diarrhœa, would come into action, which would be interfered with by the injection into the blood stream of large quantities of normal salt solution of lower salt content than the now concentrated hypertonic blood-serum. The drain through the bowel would therefore be restarted, and the restored fluid and blood-pressure rapidly lost again, as is so commonly seen in actual practice. If this view is correct, the indication would be to inject hypertonic salt solutions, so as to supply sufficient fluid to restore the circulation, and at the same time maintain the conservative beneficial hypertonicity of the blood, which would tend to carry more fluid into the circulation, instead of removing it through the damaged bowel wall. In 1907 I had an opportunity of discussing this point with both Sir Lauder Brunton, Bart., F.R.S., and Prof. Buckmaster, who were of the opinion that moderately hypertonic salt solutions might safely be injected intravenously.

The unusually great prevalence of cholera during the first half of 1908 in Calcutta furnished abundant opportunities for testing the value of intravenous transfusions of hypertonic salt solutions, for a trial of which I am greatly indebted to Captain Maxwell Mackelvie, I.M.S., who had in the meantime succeeded to the charge of the cholera wards. At first, 0·95-per-cent. sodium chloride solution was tried, and, as the results appeared to be distinctly more favourable than with the previously used 0·65-per-cent. one, it was soon raised to 1·35, or 2 drachms to the pint. The quantities injected were also raised by Captain Mackelvie to 3 or 4 pints at a time. In a note (3) published in the 'Indian Medical Gazette' in May, 1908, we recorded the results in 72 consecutive cases, in which transfusion with the above strength was used in all who required it, with a mortality of only 27·8 per cent., as compared with an average during the five years preceding the revival of transfusion at the hospital of 61·2 per cent. Moreover, at a neighbouring hospital, during the same period as our cases were treated, the mortality was just twice as great, intravenous injections not being used there, although their previous mortality during a series of years was practically the same as at the Medical College Hospital, namely, 63 against 61 per cent. At the present time our cases number 175, with a death-rate of 33 per cent., including moribund and complicated ones, which is but a very little over half that of the pre-transfusion period, although the mortality is always exceptionally high in

Table of Blood Changes in Cholera.

| | 1 Percentage of serum in the blood. | 2 Percentage loss of serum from the blood. | 3 Total loss of fluid from the blood. | 4 Pints of saline intravenously. | 5 Percentage of serum after transfusion. | 6 Blood-pressure. Before transfusion. | 7 Blood-pressure. After transfusion. | 8 Strength of NaCl injected. | 9 Percentage of chlorides in blood. Before transfusion. | 10 Percentage of chlorides in blood. After transfusion. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **I. Fatal Cases examined in Acute Stage.** | | | | | | | | | | | |
| | | | ozs. | | | | | per cent. | | | |
| 1 | 30 | 65 | 43 | 4 | 66 | 40 | 80 | 1·35 | 0·73 | 0·89 | 2nd transfusion. |
| 2 | 35 | 55 | 36 | 3 | 65 | 50 | 80 | 1·35 | — | — | 3rd transfusion. |
| 3 | 38 | 51 | 33½ | 4 | 59 | Nil | 100 | 1·35 | | | |
| 4 | 21 | 78 | 51½ | 3 | — | ,, | 115 | 1·35 | | | |
| 5 | 11 | 90 | 59½ | 4 | 50 | ,, | 110 | 1·35 | 0·67 | 0·88 | 2nd transfusion. |
| 6 | 31 | 64 | 42 | 4 | 69 | 30 | 100 | 1·35 | 1·00 | 1·09 | Very old man. |
| 7 | 39 | 47 | 31 | 4 | — | — | — | 1·35 | 0·75 | | |
| Averages | — | 64 | 42·3 | — | — | — | — | — | 0·79 | 0·95 | |
| **II. Cases of Recovery after Transfusion.** | | | | | | | | | | | |
| 8 | 42 | 40 | 26½ | 2 | 56 | — | 110 | 1·35 | 0·74 | 1·04 | |
| 9 | 34 | 58 | 38½ | 3½ | 70 | 55 | 105 | 1·35 | 0·90 | 1·27 | |
| 10 | 29 | 71 | 47 | 4 | 62 | 35 | 100 | 1·35 | — | 0·80 | Severe, 2nd transfusion. |
| 11 | 45 | 33 | 21½ | 3½ | — | 55 | 110 | 1·35 | 0·74 | | |
| 12 | 43 | 37 | 24 | 4 | 59 | — | — | 1·35 | 0·94 | 1·05 | |
| 13 | 38 | 51 | 33½ | 4 | — | — | — | 1·35 | 1·05 | 1·02 | |
| 14 | 32 | 62 | 41 | 4 | 56 | 60 | 110 | 1 35 | 1·22 | 1·25 | 2nd transfusion. |
| 15 | 36 | 55 | 36 | ? | — | — | — | — | 0·98 | 1·21 | |
| 16 | 32 | 62 | 41 | 4 | 64 | — | — | — | 0·74 | 0·86 | Severe. |
| 17 | — | — | — | ? | — | — | — | — | 0·69 | 0·99 | |
| 18 | — | — | — | 4 | — | — | — | — | 0·68 | 1·00 | |
| 19 | — | — | — | 3 | — | — | — | — | 1·22 | 1·25 | |
| Averages | — | 52 | 34 | — | — | | | | | | |
| **III. Cases of Recovery without Transfusion.** | | | | | | | | | | | |
| 20 | 43 | 37 | 24 | | | | | | | | |
| 21 | 42 | 40 | 26½ | — | — | 55 | | | | | |
| 22 | 47 | 27 | 18 | — | — | 60 | — | — | 1·06 | | |
| 23 | 49 | 22 | 14½ | — | — | 90 | — | — | 0·81 | | |
| 24 | 38 | 51 | 33½ | — | — | 80 | — | — | 0·90 | | |
| Averages | — | 35 | 23·3 | — | — | — | — | — | 0·90 | 1·07 | |

such epidemic years as the present one, and the patients were frequently too numerous to allow of as many being transfused as we should have liked. Very favourable reports have also reached me from two other medical officers who have tried hypertonic solutions in cholera.

During the last few months I have made a number of observations on the blood changes before and after transfusion in cholera, which appear to furnish a rational basis for the regular use of large hypertonic transfusions in the treatment of the disease, and propose to deal with them in the present communication. The data have all been tabulated for convenience of reference.

### *The Relationship of the Amount of Fluid lost from the Blood in Cholera to the Degree of Collapse and the Death-rate.*

As has been pointed out by Macnamara, Wall, and others, the amount of the watery evacuations in cholera will not furnish accurate data for estimating the degree to which the blood is drained of fluid, for the very rapid escape of 2 or 3 pints will have a far greater effect on the circulation than much more considerable loss spread over a longer time. Thus, in the so-called cholera sicca, in which death takes place without actual diarrhœa, the small intestines always contain several pints of liquid, the rapid draining of which from the blood has caused fatal circulatory failure. In order to ascertain the real loss of fluid from the blood in cholera, and the effects of various quantities of intravenous saline injections required to replace it, I have taken blood immediately before and after transfusion, defibrinated it at once, and measured the relative volumes of corpuscles and serum by centrifuging in the hæmocrite. As the red corpuscles are not lost to the circulation, but only the fluids of the blood, the reduction in the volume of serum can be readily calculated, and the actual loss of fluid from the serum of the blood estimated from the total volume of the blood in the body. According to some observations on healthy Bengalis by Captain McCay, I.M.S., the average proportions of corpuscles and serum respectively were 45 and 55 per cent., showing a slightly smaller proportion of corpuscles than in Europeans. Assuming that the red corpuscles are not lost from the circulation, the diminution in the serum can be calculated by the following formula from the hæmocrite figures. As the percentage volume of corpuscles found is to the normal value (45 per cent.), so is the volume of serum found to X. For example, if in a case of cholera the volume of corpuscles is 71 per cent. and of serum 29 per cent., then as

$$71 : 45 :: 29 : X, \quad \text{and} \quad X = 16.$$

That is, out of 55 original volumes of serum in the normal native blood only 16 remain, so the loss is 39 out of 55 volumes, or 71 per cent. of the total serum of the blood. In this way the figures given in column 2 have been arrived at. Further, taking the total circulating blood as one-thirteenth of the body weight (the exact amount is still disputed, but as my figures have but a relative value, this is immaterial in the present instance), I estimate the amount of blood in the body of a native of average weight as 6 pints, or 120 ounces. The percentage of serum being 55, this would give 66 ounces of blood serum in the circulation. The percentage loss in a given case having been calculated as above, the absolute loss in ounces is easily obtained, and the figures are given in column 3 of the table.

The cases have been subdivided, in accordance with the severity of the cases, into the three following classes. Firstly, those examined in the acute stage of the disease, which proved fatal from its direct effects. (Four cases in which the patients recovered from the collapse stage to die of late complications have been omitted, as the deaths were due to such affections as dysentery and parotid abscess, which afford no indication of the original severity of the cholera.) Secondly, those who showed such well-marked collapse as to require intravenous transfusion, but ultimately made a good recovery. Thirdly, milder, though well-marked, cases of cholera, in which transfusion was not necessary. The disease in most of the cases was confirmed bacteriologically, although the diagnosis was left to the physician in charge, so as to be strictly comparable with earlier series.

The average loss of fluid from the blood in each class is given in the table, and clearly demonstrates that the urgency and fatality of the cases was in direct proportion to the diminution in the volume of the blood-serum. Thus, among those in which the disease proved directly fatal, the loss of serum averaged no less than 64 per cent., or almost two-thirds, the total loss being 42 out of 66 ounces. In the second class of recoveries after transfusion there was a loss of 52 per cent. of the serum, or 34 ounces, while in the third series of recoveries without transfusion the losses averaged only 35 per cent., or 23·3 ounces.

*The Specific Gravity of the Blood in Cholera.*—The above observations furnish accurate estimations of the concentration of the blood due to loss of fluid in cholera, and demonstrate a definite relationship between its degree and the severity of the disease, while they indicate the necessity of replacing the loss in severe cases by some form of transfusion. For clinical purposes, however, some simpler method of rapidly ascertaining the required information is essential, especially in Indian hospitals far removed from laboratory conveniences. An easy, and sufficiently accurate, way is to estimate the

specific gravity of the blood by the chloroform and benzene method, or more conveniently in a hot climate by Lloyd Jones' plan of using a series of small bottles containing solutions of glycerine in water of different specific gravities, into several of which a drop of blood can be placed until the one in which it neither sinks nor rises is found. I have made a number of observations in this manner, and find that in bad cases of cholera the specific gravity usually rises over 1070, while in those which did not require transfusion it only reached up to about 1065, so that a clinically valuable approximate estimation of the concentration of the blood in cholera can thus be very rapidly obtained at the bedside. Moreover, this test can be repeated during transfusion so as to ascertain when the blood has been diluted down to its normal point, or better, a little below it, and the quantity of fluid injected can be so regulated.

*The Quantity of Fluid required to replace the Loss in Cholera.*

Columns 1 and 5 in the table show the percentage volume of serum in the blood before and after intravenous transfusion with 1·35 sodium chloride solution in the quantities indicated in column 4. The usual amount was 4 pints, and in several successful cases this quantity was repeated a second time. These are larger amounts than are usually recommended for intravenous use in cholera, but have given very good results. Moreover, column 5 of the table shows that they did not increase the volume of serum very materially above the normal level of 55 per cent., while any excess will pass rapidly into the greatly drained tissues, and some allowance must be made for further losses through the bowel before the disease completely subsides. In several cases the blood was found to have again become so concentrated by the following day as to necessitate a second injection, with ultimate recovery, so that the amounts used were certainly not excessive. At the same time there must be a limit to the quantities that can be rapidly administered intravenously at one time, and the fact that in several cases the volume of serum was raised to between 65 and 70 per cent. appears to indicate that 4 pints is sufficient in most cases. In the very exceptional concentration of the blood in case 5, however, even this amount failed to increase the serum even to the normal point, the specific gravity after the injection being also 1064, or considerably above the normal, and the patient ultimately died.

In the less severe types much fluid can be got into the system by rectal injections, which are of great value. Subcutaneous injections are often used, but act much more slowly than intravenous ones in raising the blood-pressure, and are very liable to be followed by abscess in the low state of

vitality of the tissues in cholera. I have recently had a simple cannula constructed with circular end sharpened like a cork borer, which can be safely passed through the abdominal wall after incising the skin and fascia. By this means saline fluid can be rapidly run directly into the abdominal cavity, and it has been successfully used in a number of cholera cases in one of the Calcutta hospitals. It can also be carried out in a much shorter time than the more difficult operation of tying a cannula into the collapsed vein of a cholera patient, but it takes several hours to be absorbed, so is less efficient in urgent cases than the intravenous injections. The hypertonic solutions have been found to give better results than normal saline by all methods of administration.

*The Loss of Chlorides from the Blood in Relation to Hypertonic Transfusions.*

Edmund Parkes, in 1849, showed that the rice-water stools of cholera contain very little albumen, but from $\frac{1}{2}$ to 1 per cent. of salts, so that for every hundred ounces of fluid evacuations from the bowel nearly an ounce of salt is lost from the blood and tissues. The main bulk of the salts consists of chlorides, which may be taken as a guide to the amount in the blood at any time. Some recent estimations made by me gave an average of 0·53 per cent. of chlorides in cholera stools. The vomited matter contains much less salt than the bowel discharges, apparently owing to the gastric mucous membrane being less involved in the disease processes than the intestinal. Different observers have obtained very varying results as regards the percentage of salts found in the blood in cholera, some maintaining that they are higher, and others lower, than normal, but the observations on this point in the very limited literature available in Calcutta were all made many years ago. I have, therefore, estimated by the silver nitrate method the amount of chlorides in the blood in a number of cases both before and after transfusion with the 1·35-per-cent. sodium chloride solution. The results are shown in columns 9 and 10 of the table.

Taking first cases 1—7, which were fatal in the acute stage, we must bear in mind that on the average two-thirds of the fluid had been lost from their blood. If only the water had been removed without any saline constituents, then the chlorides should have been present in three times the normal amounts. The percentage of salts in the blood in Bengalis has been found by Captain McCay to be somewhat higher than in Europeans, namely about 1 per cent., about 0·8 per cent. of which are chlorides. Yet in the fatal cholera cases, in spite of the great concentration of the blood, the chlorides were below the normal in four out of five, the single exception being a very old man who died of heart failure. Fully two-thirds of the total chlorides of

the blood must, therefore, have been lost. In case 5, with only 0·67 per cent. of chlorides, the serum showed actual commencing hæmolysis, which completely disappeared when they had been raised to 0·88 by hypertonic transfusion, while similar results have been noted in a few other cases with very low salt content. Column 10 shows that a material rise in the percentage of chlorides in the blood was obtained by transfusion of 3 to 4 pints of 1·35-per-cent. sodium chloride solution, but the average amount after it was still only 0·95 per cent.

On turning to the recovering cases 8 to 24, we find the average percentage of chlorides in the blood before transfusion was 0·90, or considerably higher than in the fatal series, and the same remark applies to the figures obtained after transfusion, when the average was 1·07 per cent. Moreover, in cases 10 and 16, which showed a low amount of chlorides after the injection, the disease was very severe, and in one a second transfusion was necessary to save the patient. It will be observed that several of the cases, which recovered after the injections, showed very low chlorides in the blood at the first estimation, but when they were raised to about 1 per cent. or over by the hypertonic solutions, the patients almost invariably did well as far as the collapse stage of the disease was concerned, which is the most dangerous period in cholera.

Another striking feature was the far less tendency of the hypertonic solutions to restart the copious rice-water stools, which so commonly renders the use of normal salines of such very temporary value. It is not too much to say that at the Medical College Hospital, where cholera patients are usually brought in an advanced stage of collapse, the simple substitution of 2 drachms of salt to the pint instead of one, for transfusion, has so revolutionised the treatment, that, whereas formerly it was considered a matter for surprise when a severe case of cholera recovered, it is now a great disappointment when such a case is lost in the collapse stage.

### *The Coagulability of the Blood in Cholera.*

A few observations on the clotting power of the blood have been made by Sir Almroth Wright's method. The results were very variable, the time being normal in some, slightly reduced in most, and very markedly in a few. It is noteworthy that in several of the worst cases, with a specially low percentage of chlorides, blood taken in glass tubes remained quite uncoagulated after several hours, and in one such case there were hæmorrhagic stools, found *post mortem* to be dependent on extensive petechial hæmorrhages in the cæcum. After transfusion with hypertonic solutions the blood in such cases clotted firmly and gave a clear serum. In view, however, of the

frequency of reduction of the clotting power of the blood in cholera, I now add 3 grains of calcium chloride to each pint of salt solution, and have seen no hæmorrhagic stools in the few cases since treated.

*Strength of the Hypertonic Solutions.*

In a few cases, 1·65-per-cent. solution (2½ drachms to the pint) were used with good results, but as the 1·35 per cent. has proved successful in so many cases, and, moreover, suffices to raise the chlorides in the blood well above the normal, it is recommended for routine use. The higher strength may be reserved for second transfusions in very severe cases, or when the lower strength has not increased the percentage of chlorides in the blood to the desired point of 1 per cent. or over, and especially if watery diarrhœa continues. We have never seen any harm from running these solutions rapidly into a vein in cholera, 4 pints having frequently been administered in 20 minutes. The specific gravity of the 1·35 solution is 1006, and of 1·65 is 1008, a knowledge of which allows the strength of the solution to be rapidly verified.

*Effects of Intravenous Saline Injections on the Blood-pressure.*

The blood-pressures immediately before and after transfusions are shown in columns 6 and 7 of the table. Nil means that there was absolutely no pulse at the wrist, so it could not be recorded in the radial artery, which was the site of the other observations. It usually required about three pints to raise the blood-pressure to 100 mm., which is the normal for Hindus. Experience showed that the best results were obtained by continuing the injections until the pressure rose somewhat above that point, for which purpose 4 pints were generally necessary, and allow some reserve. In some of the worst cases it was impossible to get it above 80 mm., as in numbers 1 and 2 in the table, for it remained at that point in spite of another pint being run in. One instance was met with in which even 6½ pints failed to raise the pressure above 65 mm. In such there appears to be some vasomotor paralysis present, possibly due to absorption of albumoses through the damaged intestinal mucous membrane. Adrenalin forces up the pressure in them, but its effects are only very temporary, as I formerly found it to be in the vasomotor paralysis of viperine snake poisons (4). The blood-pressure, then, is a valuable guide to the amount of saline solution to be run in, a pressure slightly above the normal being aimed at; but if 4 or more pints have been given, and the last 20 ounces or so have produced no further improvement, it is useless to continue it at that time. Fortunately a degree of vasomotor paralysis which prevents the pressure being raised to 90 or 100 mm. in natives of India is rare, as such have always terminated fatally in my experience.

*The Relationship of Blood-pressure to Post-choleraic Uræmia.*

One result of tiding so many severe cases of cholera over the collapse stage by large hypertonic saline transfusions, is to accentuate the importance of uræmia in the later stages of the disease. This very serious complication is especially seen in two distinct classes of cases :—Firstly, in patients brought to hospital more than 48 hours after the onset of the symptoms, which not infrequently have been comparatively mild at the onset, and whose treatment has been neglected. Secondly, the other extreme of patients admitted early on account of the great severity of the affection, who have been supported by repeated transfusions to the stage of reaction, when it is found to be extremely difficult to restore the renal secretory activity, which has been in abeyance during the prolonged period of very low blood-pressure.

On cutting sections of the kidneys of patients who had died in the uræmic stage of cholera, I was much struck by the amount of effused blood in and around the convoluted and straight tubules and the tense state of the capsule enclosing the extremely congested organ : all suggesting an actual mechanical difficulty in the re-establishment of an efficient circulation through the organ. In order to test if this was the case or not, I tried perfusion of normal saline solution through the renal artery from different heights, so as to measure the actual pressure required to obtain a fairly full outflow from the renal veins. For this purpose I used both healthy kidneys, got from the bodies of patients dying of other diseases, and also several from those who had succumbed to the uræmia of cholera. In the former, a pressure equivalent to 20 or 30 mm. of mercury sufficed to obtain a good flow through the kidney circulation. On the other hand, in the cholera ones no flow at all was got under a pressure of about 60 mm., and then only drop by drop, and it was not until 90 or 100 mm. was reached that anything like a full stream was observed. In one experiment, subsequent slitting of the capsule of the organ reduced the pressure required by about 20 mm. In a case of cholera in which the patient died of late complication with empyema, after the secretion of the urine had been freely established a pressure equivalent to 30 mm. of mercury sufficed for the free perfusion of normal saline through the kidneys, showing that it was only in uræmic cases that obstruction of the renal circulation existed in such a marked degree.

Since the above observations were made, the blood-pressure has been carefully watched day by day after the termination of the collapse stage, and it has been found that the uræmic symptoms are more common in those whose blood-pressures do not rise above 100 mm. For example, two very severe cases of cholera were admitted to hospital at about the same time, both of whom received two saline transfusions of 4 pints each, and

recovered from the collapse stage. On the fifth day both had passed little or no urine and showed definite uræmic symptoms. The blood-pressure of one was now only just 100 mm. and he died the following night of uræmia. That of the other was 120 mm., and he began to pass urine that day, and made a good recovery. Soon after another patient developed well-marked uræmia, his respirations being over 40 per minute and very laboured, while he was practically unconscious, and apparently in a hopeless state. As his blood-pressure was found to be only just 100 mm., adrenalin and digitalis were administered subcutaneously, and on the following morning his pressure was 110 mm., he had recovered consciousness, was passing urine freely, and got well from that time. Thus, the indications derived from the *post-mortem* kidney perfusion experiments have been borne out in practice, and it is clear that the blood-pressure is the most important factor to be attended to in the treatment of the deficient renal secretion, which ensues in so many severe cholera cases, after the danger of death from collapse has been averted by saline transfusions.

*Conclusions.*

1. In cholera there is a very definite relationship between the amount of fluid lost from the blood and the severity and mortality of the disease.

2. This loss is usually so great as to indicate saline transfusions to restore the circulation.

3. Injections of normal salt solutions are commonly of only very temporary benefit.

4. Hypertonic salt solutions (1·35-per-cent. sodium chloride, or 2 drachms to the pint) are much more effective, their use having reduced the mortality by about one-half.

5. A great loss of chlorides from the blood occurs in cholera, most marked in the worst cases. If the percentage of chloride is considerably raised by the intravenous injection of hypertonic salt solutions recovery usually ensues.

6. The development of uræmia in the reaction stage of cholera is associated with a comparatively low blood-pressure, measures to raise which are indicated for the prevention and treatment of this very serious complication.

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